PARADIGM BIOPHARMA

Top-line Results Presentation

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Exec Summary

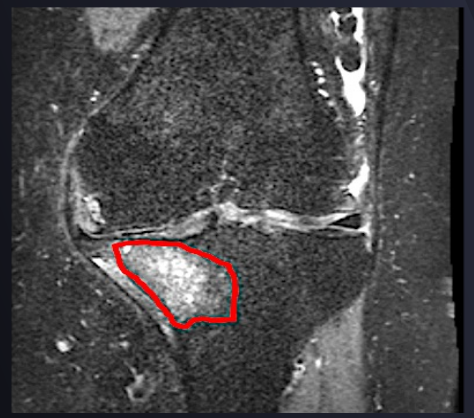
PARA_OA_008 Key Highlights

- Primary endpoint achieved as several favourable synovial fluid biomarker changes were observed in injectable PPS-treated patients compared to placebo.
  - Reduction in NFG, TNF-α, IL-6, COMP, and ARGS;
  - Increase in TIMP-1.
- PPS-treated subjects demonstrated statistically significant changes in WOMAC pain, function, stiffness, and overall WOMAC score compared to placebo at day 56.
  - The proportions achieving ≥30% and ≥50% improvement in pain were 73% and 60%, respectively, in the twice-weekly iPPS group.
- No serious adverse events and no adverse events of special interest were observed in any patient receiving iPPS or placebo.

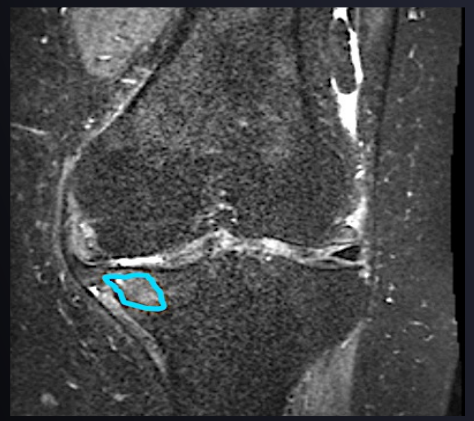
Why was the study conducted?

Phase 2b – PARA_OA_005 (2 mg/kg SC twice weekly v placebo)
PPS showed significantly reduced serum levels of cartilage degradation biomarkers and significant reduction in BML size as compared with placebo controls.

Reduction in size of **Bone Marrow Lesions**

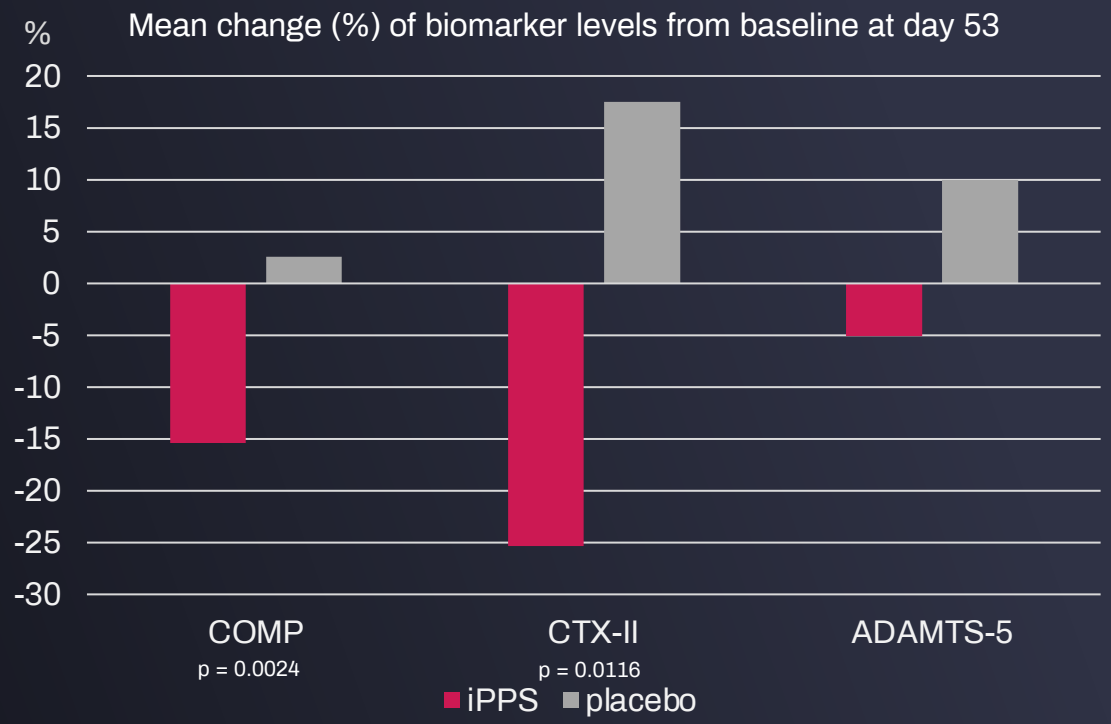


Grade 3 medial tibial BML at baseline



Grade 2 medial tibial BML at follow-up day 53

Reduction in serum levels of **COMP, ADAMTS-5** & urine levels of **CTX-II**



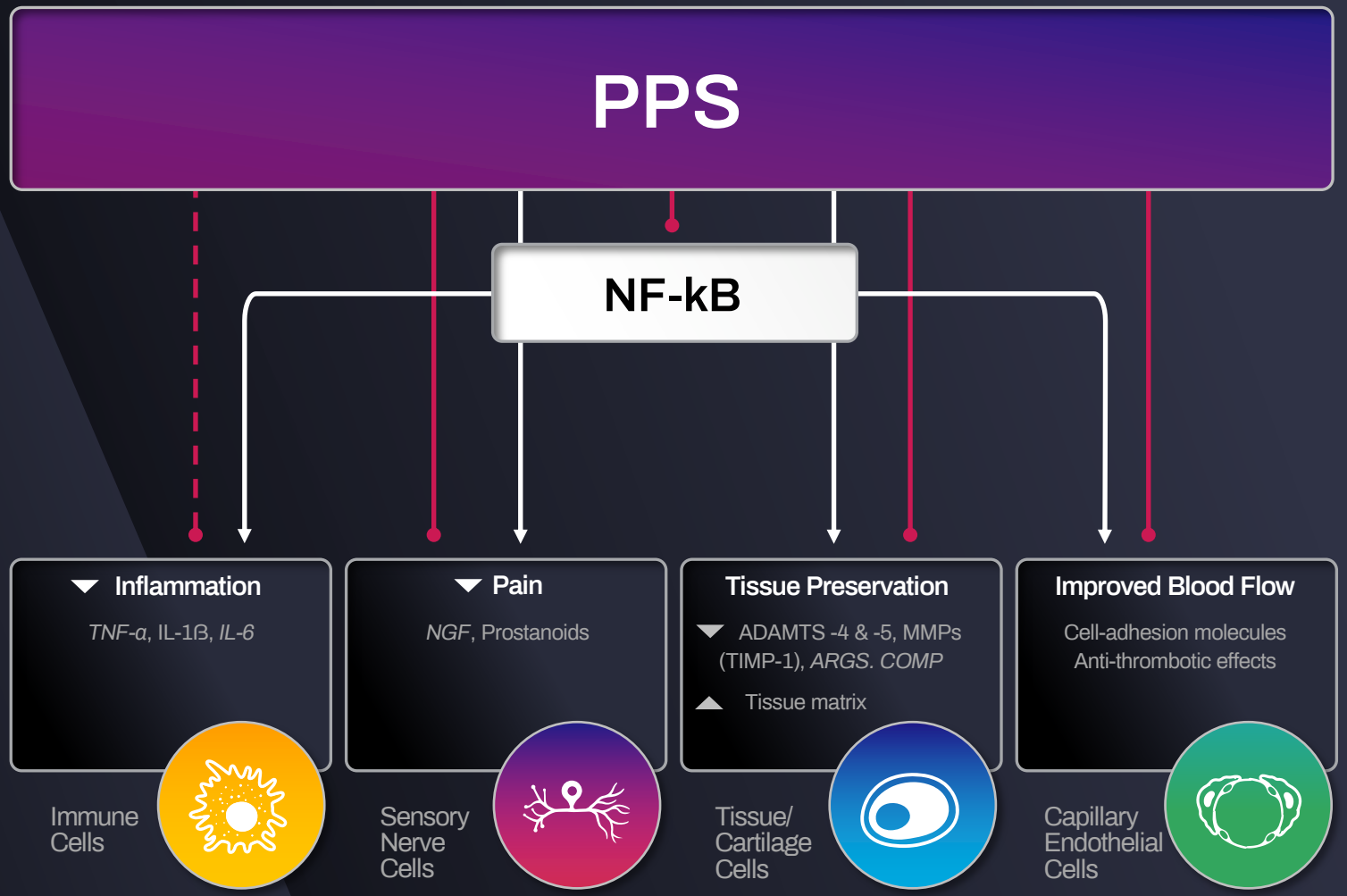
Among subjects with symptomatic knee OA, **a single measurement of increased COMP predicted subsequent cartilage loss on MRI**. (Hunter et al. 2007)

Mechanism of action

- Multiple modes of action
- Previous phase 2B, SAS, and EAP experience
- New phase 2 data

OA
MPS
ARDS
HFpEF
Alphavirus Induced Arthralgia

Current hypothesis for PPS mechanism of action



PARA_OA_008 Phase 2 Clinical Trial

Study Design

- To evaluate the treatment effects of injectable PPS on synovial fluid biomarkers associated with OA-related pain, inflammation, and disease progression.
- Sixty-one subjects (n=61) were randomised 1:1:1 to receive either subcutaneous injection of 2 mg/kg PPS twice weekly, once weekly + one placebo injection, or two placebo injections, for 6 weeks.
- The Australian clinical trial is being run at two sites in Vic and NSW and aims to gather data on the medium to long-term structure-modifying and symptom-modifying effects of iPPS on knee OA.
- The primary endpoint is change from baseline at day 56 (two weeks post final injection) in one or more synovial fluid biomarkers associated with disease progression in OA.
- The phase 2 trial is assessing a number of key secondary and exploratory endpoints at various timepoints out to 1 year including, WOMAC pain and function data, MRI changes in the bone and joint, and correlations between synovial fluid changes and clinical outcomes (pain and function).

Synovial Fluid Biomarkers

Day 56 Top-line Results – Changes in Synovial Fluid Biomarkers

- iPPS impacted multiple biomarkers measured in the synovial fluid:
  - NGF reduction indicates mechanisms relating to pain reduction;
  - Reductions in TNF-α and IL-6 indicate mechanistic effects on inflammatory pathways;
  - Reductions in COMP and ARGS and increases in TIMP-1 provide important insights on iPPS mechanisms impacting cartilage preservation.

- In all cases, the synovial biomarker changes in iPPS-treated subjects at day 56 were favourable compared to placebo control.

Clinical Outcomes

Day 56 Top-line Results – Changes in WOMAC Pain and Function from Baseline

- Participants in the study were asked to provide baseline pain scores using the WOMAC Osteoarthritis Index.
- iPPS treatment showed statistically significant improvements at day 56 in pain, function, stiffness, and overall WOMAC scores for twice-weekly iPPS compared to the placebo arm.
  - The mean percentage change from baseline in WOMAC pain is 50% compared to 30%, p=0.05 for twice weekly iPPS and placebo.
  - The mean percentage change from baseline in WOMAC function is 50% compared to 25%, p=0.017 for twice weekly iPPS compared to placebo.
  - The proportions achieving ≥30% and ≥50% improvement in pain were 73% and 60%, respectively.
- The reduction in pain for iPPS-treated subjects are consistent with the clinical effects observed in this and prior studies of iPPS in osteoarthritis.

Naturally Occurring OA Canine Model

Study Design

- To support the in vivo mechanism of action of PPS for disease modification and provide complimentary data to parallel the PARA_OA_008 human clinical trial, Paradigm is also conducting a trial in dogs with naturally occurring OA.
- 21 dogs with OA of either the hind limb or front limb joint, randomised 2:1 are treated with PPS at a dosing of 3 mg/kg (1.7 mg/kg human equivalent) or placebo by subcutaneous injection weekly for 6 weeks.
- The key data sought from this study are changes from baseline at week 8 (day 56) and week 26 (equivalent to 3 years in human terms), in:
  - Joint function is assessed by percentage body weight distribution in the affected limb, as measured by the total pressure index percentage (TPI%);
  - Biomarkers of joint degeneration within the synovial fluid and in the serum *and;*
  - Structural changes determined by OA clinical scores as assessed by X-ray and MRI.

Naturally Occurring OA Canine Model

Week 8 (2 weeks following final injection)

Early interim functional observations in nine osteoarthritic dogs:

- 7/9 dogs treated with PPS had a clinically meaningful improvement in the affected limb as measured by TPI% at week 8 compared to baseline.
- Mean percentage change (improvement) from baseline in TPI% of 10.08% was observed for the affected hind limb (n=5) and 5.6% for the affected front limb (n=4).
- A mean increase of 5% in TPI% is a clinically meaningful improvement.

Naturally Occurring OA Canine Model

Week 8 (Day 56) Observations

Early biomarker observations in osteoarthritic dogs:

- Hyaluronic acid (HA) and aggrecan degradation neoepitope (ARG) are cartilage degradation biomarkers:
  - 3/4 had reduced levels of aggrecan degradation neoepitope (ARG)*;
  - 4/4 had reduced levels of hyaluronic acid (HA) in the synovial fluid.
- Reduction in ARG levels within the synovial joint supports the *in vivo* MoA since PPS inhibits ADAMTS-5 enzyme which degrades aggrecan in cartilage to produce ARG.
- Degrading cartilage matrix releases HA into the synovial fluid in OA and which is reduced by PPS as shown in this study.
- Analysis of serum biomarkers demonstrated that 3/6 dogs showed a reduction in serum ARG, and 5/9 dogs had reduced serum HA, supporting the effect of iPPS on these biomarkers observed in the synovial fluid.

*ARG is the canine equivalent of human ARGS

6-Month Follow-Up

What we expect to report

PARA_OA_008

- Durability of effect in clinical outcomes (WOMAC pain, function, stiffness and PGIC).
- Changes and correlation between synovial fluid, serum, and urine biomarkers and correlation with changes in clinical outcomes.
- MRI changes in the bone and joint.

Canine OA Model (3-year human equivalent)

- Durability of effect of joint function.
- Biomarker changes within the synovial fluid and in serum.
- Structural changes determined by OA clinical scores as assessed by X-ray and MRI.

Upcoming Catalysts

Near-term news flow

- PARA_OA_002 update – First data safety monitoring board review Q4 CY2022
- PARA_OA_006 extension study commencement Q4 CY2022
- FY22 tax rebate Q4 CY2022
- Further IP generation and protection
- MPS-I data presented at International Conference on Lysosomal Diseases Q1 CY2023
- PARA_OA_008 6-month data Q1 CY2023
- Canine OA Model – 26-week (3-year human equivalent) data 1H CY2023
- PARA_OA_002 Stage 1 dose selection 1H CY2023.
- Paradigm is currently in active discussion with multiple potential partners for its phase 2 asset in mucopolysaccharidosis (MPS).

For more information please visit:
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